Hepatology Snapshot

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Snapshot liver transcriptome in hepatocellular carcinoma

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Background

Hepatocellular carcinoma ranks among the most common cancers worldwide. However, besides surgery, therapeutic strategies remain limited and a detailed analysis and characterization of the tumor biology will be essential in order to identify (novel) therapeutic targets [1]. With the development of sorafenib, a first step of successful targeting molecular changes in HCC has been made but many more will have to follow in order to establish a potent arsenal of specific therapeutic options [2].

Transcriptome studies

Lately, advances in high throughput technologies in biomedical research have led to a dramatic increase in the accessibility of molecular insights at different levels of cancer biology such as genome, epigenome, transcriptome, proteome, and others. Among the diverse biological layers, the transcriptome has been most extensively studied especially due to the successful and broad introduction of the microarray technology. The future prospect of broad disposability of deep sequencing technology will furthermore lead to a more sensitive detection of lowly expressed transcripts and to an increase in the number of newly identified transcripts, but also to increase the discovery and characterization of alternative splicing. A common goal of large scale transcriptome profiling methods is the stratification of patients, eventually leading to personalized prognostic predictions and therapeutic strategies. Also, the observation that diverse etiologies of the mostly underlying liver cirrhosis (alcohol, HBV, HCV a.o.) are represented by different transcriptome profiles may be valuable for the identification of essential tumor targets [3]. In particular, the field of biomarker discovery and development make considerable use of microarray technologies for clinical research [4]. In breast cancer, this vision was enthusiastically pursued over the past several years resulting in an FDA-approved molecular signature, which may serve as an example [5].

It has repeatedly been reported that transcriptomic changes not necessarily reflect changes in the corresponding proteins. In model organisms, approximately 25% of changes in gene expression are not accompanied by simultaneous changes in protein abundance, particularly of lowly expressed genes [6]. It has also been observed that the transcriptome of hepatocellular carcinoma often includes surgical material, which has not been subjected to laser capture microdissection. The current data on the transcriptome of hepatocellular carcinoma are, therefore, diluted by cells present in the tumor microenvironment. However, a recent publication by Villanueva *et al.* demonstrated the usefulness of integrating transcriptomic signatures with clinic-pathological data in HCC and in particular demonstrated partial reproducibility in independent data sets [7].

Influencing gene expression in HCC

Multiple biological mechanisms were shown to change gene activity in HCC. Among them are changes in chromosomal structure, genetic polymorphisms, alternative splicing, epigenetic changes (methylation, histone modification, miRNAs), and proteomic changes. Therefore, we present a short graphical snapshot of the liver transcriptome in HCC (Fig. 1).

Chromosomal structure and gene polymorphisms

Changes in chromosomal structure have been extensively described. Obviously, lack or duplication of genetic regions and thus of genes physiologically involved in liver homeostasis may result in disturbed gene expression, which potentially favors hepatocarcinogenesis. Several studies reported correlations of single chromosomal gains or losses with clinicopathological features such as tumor differentiation or prognosis (reviewed in [8]). Furthermore, high density allelotyping using a large number of microsatellite markers combined with gene mutation analysis led to identification of diverse genetic pathways involved in HCC [9] (Table 3).

Promoter methylation

DNA methylation in the promoter region of a gene may be linked to altered gene expression. Hypermethylation of tumor-suppressor genes as well as genes involved in cell cycle regulation, apoptosis, DNA repair or cell adhesion, and DNA methylation plays a crucial role in the development of a variety of cancers. Accordingly, hypomethylation and consecutive activation of oncogenes was also recognized to potentially result in cancer development. Over the past several years, multiple genes exhibiting changes in promoter methylation in HCC were identified (Table 4, [10]).

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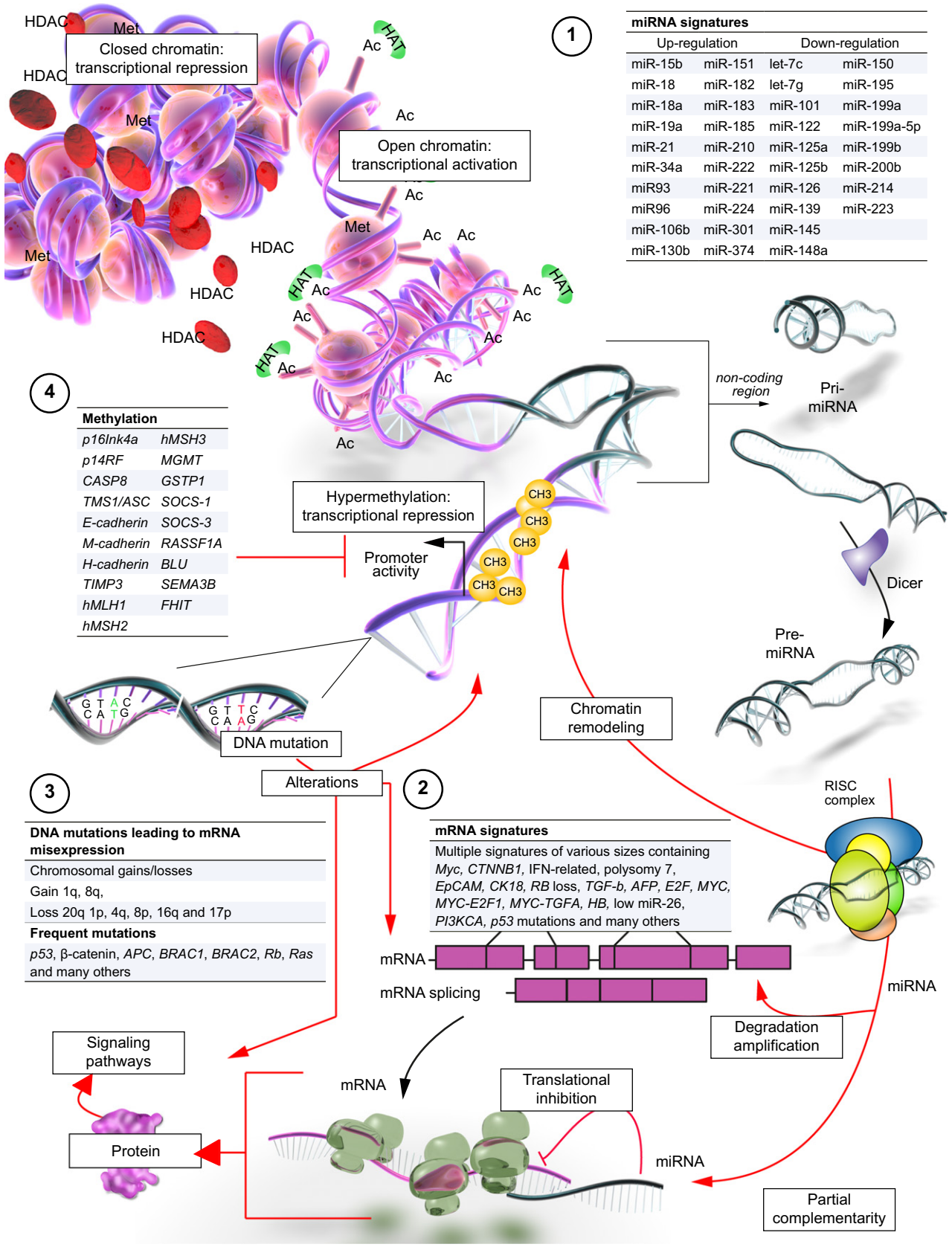

Fig. 1. Snapshot of the liver transcriptome in HCC providing a comprehensive overview on the complex interaction of diverse biological layers.

In hepatocarcinogenesis, changes in DNA methylation must be considered to occur frequently and early. Furthermore, changes in the methylation status may accompany the progression from precancerous lesion to HCC. Finally, some of these changes were even demonstrated in premalignant conditions, such as liver cirrhosis [10].

Histone modification

Histone acetylation is dependent on the equilibrium between the activities of histone acetyltransferases and deacetylases (HDAC), linking acetyl groups to lysine tails. Histone hyperacetylation is associated with a less condensed chromatin structure and thus and unfolded, more easily transcribed DNA. In HCC, evidence for efficacy of HDAC inhibitors stems from preclinical and preliminary clinical phase I and II trials. Among the molecular changes induced through changes of histone acetylation were cell cycle related proteins, such as p21waf1 and p27kip1, and cyclin D1. Lee *et al.* reported that changes in histone modification may be associated with patients prognosis, with higher levels of genes involved in histone modifications in HCC with poor outcome [11]. Thus, the concept of inhibiting histone acetylation will be interesting to follow in the coming years [10,12].

miRNA expression

The discovery of microRNAs (miRNAs) introduced an additional layer of complexity to transcriptome regulation. These small RNAs are non-coding but have the capacity to target multiple genes simultaneously. It has been well established that dysregulation of miRNAs is essential for the development of various cancers. Given their broad transcriptome interference, these molecules may represent promising targets for therapeutic intervention. In addition, both single miRNA and small cluster of miRNAs may be of prognostic value in HCC [13].

Conclusions

Over the past decade, modern molecular biology and the use of high throughput genomics and transcriptomics have identified multiple biological layers involved in transcriptome regulation. Unraveling the tight and complex interactions between diverse molecules, data and involved biological layers in transcriptome of the HCC tissue will certainly result in a much better understanding of the underlying biology. Thus, bringing together the diverse aspects of transcriptomic changes in HCC will lead to a whole new perception of HCC development and subsequently disclose novel strategies for the diagnosis and treatment of HCC.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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